REMARKS

I. Status of the Claims

Claims 1 and 19-34 are pending in the application, and claim 1 stands withdrawn. Claims 19-34 are thus under examination and stand rejected, variously, under 35 U.S.C. §112 (second paragraph), §102 and §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Objections

Claims 24-26 and 29-34 remain objected to because of inclusion of non-elected subject matter. Additional amendments are believed to address the objection, reconsideration and withdrawal of which is therefore respectfully requested.

III. Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 22, 23, and 28 remain rejected as indefinite. Applicants traverse, but in the interest of advancing the prosecution, claims 22 and 23 have been canceled, and claim 28 has been amended to address the examiner's concerns. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Rejections Under 35 U.S.C. §102

Claims 19, 22, 23, 27 and 28 remain rejected as anticipated by Hoon *et al.* Applicants traverse, but in the interest of advancing the prosecution, claim 19 has been amended to include the two of the specific primers from claim 20, which was not rejected over this reference. As such, it is believed that the rejection is overcome.

Claims 19, 22, 23 27 and 28 remain rejected as anticipated by Kirken *et al.* Applicants traverse, but in the interest of advancing the prosecution, claim 19 has been amended to include the two of the specific primers from claim 20, which was not rejected over this reference. As such, it is believed that the rejection is overcome.

Reconsideration and withdrawal of each of the preceding rejections is therefore respectfully requested.

V. Rejections Under 35 U.S.C. §103

The PTO bears the burden of establishing a case of *prima facie* obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). To make out a case of obviousness, one must:

(A) determine the scope and contents of the prior art;

(B) ascertain the differences between the prior art and the claims in issue;

(C) determine the level of >ordinary< skill in the pertinent art; and

(D) evaluate evidence of secondary considerations if a *prima facie* case is established.

Finally, Office personnel should evaluate the totality of the facts and all of the evidence to determine whether they still support a conclusion that the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. *Id.*

A. Kirken *et al.*

Claims 20, 21 and 24 stand rejected as obvious over Kirken *et al.* Applicants again traverse.

Kirkin provides a pharmaceutical composition for inducing an immune response in a human or animal. To this end, dendritic cells are loaded with at least five cancer/testis antigens and no lineage specific differentiation antigens, wherein the cancer/testis antigens are provided from at least one cancer cell line. In Example 1, Kirkin describes a conventional RT-PCR approach using oligo-dT primers for first strand synthesis, followed by PCR using separate, specific primer pairs for the amplification of the cDNA, *e.g.*, of MAGE A1 (see para 0144). RT-PCR has been carried out to analyse expression of MAGE genes in a melanoma cell line. However, Kirkin fails to teach/suggest a pan-MAGE cDNA primer which allows first strand synthesis and detection of all MAGE mRNA subtypes. In particular, Kirkin does not teach/suggest the pan-MAGE cDNA primer MgRT3a (SEQ ID NO:4) as now claimed.

As shown in Example 2 of the present application, MgRT3a is the only gene specific cDNA primer (*i.e.*, no conventional hexamer primer, no oligo-dT primer normally used for cDNA first strand synthesis) of a series of primers tested that functions as a highly sensitive pan-MAGE cDNA primer. In particular, MgRT3a allows the sensitive detection of MAGE-1, MAGE-2, MAGE-3/6, MAGE-4 and MAGE-12 mRNA subtypes, as exemplified in a 2 ml blood sample containing no more than five tumor cells (see also Table 3)! This means that MgRT3a simultaneously hybridizes to five different MAGE gene transcripts. In the absence of any motivation with regard the provision of a pan-MAGE cDNA primer, it was not obvious for the person skilled in the art to arrive at MgRT3a, in light of Kirkin alone. In addition, there was no reasonable expectation of success since MgRT3a was the only primer of a series of primers capable of hybridizing to all MAGE transcripts.

Further, with respect to claim 21, in order to quantify MAGE expression in comparison to the expression of a housekeeping gene, PBGD primers have been tested as internal calibrators.

As shown in Example 3, thirty-two PBGD primers have been tested, only one of which did not disturb the reverse transcription of MAGE mRNAs. It was only the PBGD_RT15b (SEQ ID NO:35) primer which was found to work effectively in combination with the pan-MAGE cDNA primer MgRT3a; see Example 3 and Table 9. This result could not have been predicted, and thus provides a further point of patentability for any claim reciting this element.

Thus, because the cited reference fails to provide a teaching of each element of the claimed invention, *i.e.*, the primers MgRT3a and PBGD_RT15b, it cannot render the claims obvious. Reconsideration and withdrawal of the rejections is therefore respectfully requested.

B. Kirken *et al.* in view of Scanlan *et al.* and Buck *et al.*

Claims 25 and 26 remain rejected as obvious over Kirken *et al.* in view of Scanlan *et al.* and Buck *et al.* Applicants traverse, but in the interest of advancing the prosecution, the claims have been canceled.

C. Hoon *et al.*/Kirken *et al.* in view of Gellerfors *et al.* and Sagner *et al.*

Claims 29-32 are rejected as obvious over Hoon *et al.* or Kirken *et al.* in further view of Gellerfors *et al.* and Sagner *et al.* Claims 29 and 32 have been canceled, leaving claims 30 and 31 as rejected. The teachings and deficiences of Kirken are set out above. Like Kirkin, Hoon describes a conventional RT-PCR approach using oligo-dT primers for first strand synthesis, followed by PCR using separate specific primer pairs for the amplification of, *e.g.*, MAGE 1 or MAGE 3; see Example 1, columns 15 and 16 and Example XIII. However, Hoon fails to teach/suggest the pan-MAGE cDNA primer MgRT3a which allows first strand synthesis and highly sensitive detection of all MAGE mRNA subtypes.

Gellefors describes PBGD DNA sequences, such as SEQ ID NO. 7, which is the PBGD DNA sequence from bone marrow. In addition Gellefors describes four PBGD primers (Ico375, 376, 379, 382) which can be used as PCR amplification primers or for sequencing purposes (Table 1). The examiner argues that the use of applicants' PBGD_RT15b (SEQ ID NO:35), which is allegedly embedded in much larger sequences disclosed by Gellefors, is rendered obvious by this reference. Applicants submit that this is incorrect. There is no identification of the discrete PBGD_RT15b primer in the cited reference, nor is there motivation to use PBGD_RT15b as part of a diagnostic composition. It simply is not enough, in the context of obviousness, that the art generically points to PBGD as a marker of interest. Gellefors clearly fails to teach/suggest the specific sequence of PBGD_RT15b (SEQ ID NO. 35) of the present invention, let alone a specific combination of primers MgRT3a ***and*** PBGD_RT15b. The same holds true for Sagner.

In the present invention, a series of PBGD primers have been tested as internal calibrators in order to quantify MAGE expression in comparison to the expression of a housekeeping gene. As shown in Example 3, thirty-two PBGD primers have been tested, only one of which ***did not*** disturb the reverse transcription of MAGE mRNAs. It was only the PBGD_RT15b (SEQ ID NO:35) primer which was found to work effectively in combination with the pan-MAGE cDNA primer MgRT3a (*see* Example 3 and Table 9). This result could not have been predicted, and thus provides a further point of patentability for any claim reciting this element.

Thus, because the cited reference fails to provide a teaching of each element of the claimed invention, *i.e.*, the primers MgRT3a and PBGD_RT15b, it cannot render the claims obvious. Moreover, there was no reasonable expectation of success for the person skilled in the

art to arrive at such a specific primer combination in light of the teaching of the art. Reconsideration and withdrawal of the rejections is therefore respectfully requested.

D. Hoon *et al.*/Kirken *et al.* in view of Boon-Falleur *et al.* and Buck *et al.*

Claim 33-34 are remain rejected as obvious over Hoon *et al.* and/or Kirken *et al.* in further view of Boon-Falleur *et al.* (U.S. Patent 6,221,593) and Buck *et al.* (Biotechniques, Sept. 1999, Vol. 27, No. 3, pp. 528-536). Claim 34 has been canceled, leaving claim 33 rejected. The teachings and deficiencies of Kirken and Hoon are discussed above. Boon-Falleur *et al.* teach PCR-primers for PCR-amplification of MAGE-A10 from cDNA obtained through reverse transcription using ***unspecific priming*** (Boon-Falleur *et al.*, column 9, Example 11, lanes 16-20).

In contrast, claim 33 teaches PCR-primers, which are different in sequence from those taught by Hoon, Kirken or Boon-Falleur, for PCR-amplification of MAGE-A10 from cDNA obtained through ***specific priming*** by at least one MAGE cDNA-primer (see above). Actually, the MAGE-A10 primers of claims 33-34 were selected among those particularly suited for PCR-amplification from cDNA obtained through ***specific priming*** by at least one MAGE cDNA-primer, for achieving the highest sensitivity for detection of rare tumor cells by the real-time RT-PCR of the present invention (US2006/0147928 Example 10, Tables 10 and 11). This selection could be predicted from Boon-Falleur alone because it relates to unspecific instead of specific cDNA-priming, nor in combination with Buck *et al.*, as explained below.

Buck *et al.* describes a study which surveyed strategies of sequencing primer selection and evaluated primer performance in automated DNA sequencing. The authors asked participants to relate their preferred primer design strategies to identify primer characteristics that are considered most important in sequencing primer design. The participants preferred primers of 18-24 nucleotides (nt), 39%-58% G + C, a melting temperature (Tm) of 53-65°C with a 1-2 nt 3'

GC clamp, hairpin stems of less than 2-3 bp, homopolymeric runs of less than 4-5 nt, primer dimers of less than 3-4 bp and secondary priming sites of less than 3-4 bp. However, Buck fails to suggest specific cDNA primers which are capable of hybridizing to at least two MAGE gene transcripts, let alone the suggestion of MgRT3a and PBGD_RT15b.

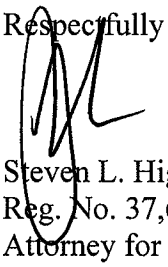
Thus, the cited references, even when taken in combination, fail to provide any suggestion or motivation to arrive at a diagnostic composition comprising the primer MgRT3a. Therefore claims 25 and 26 are not obvious over the cited art. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Reconsideration and withdrawal of the rejections is therefore respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at 512-536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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